

**NOVEL ESTER DERIVATIVES OF BUPRENORPHINE AND THEIR
PREPARATION PROCESSES, AND LONG ACTING ANALGESIC
PHARMACEUTICAL COMPOSITIONS**

BACKGROUND OF THE INVENTION

5 **1. Field of the Invention**

 The present invention relates to novel ester derivatives
of buprenorphine, in particular buprenorphine
monocarboxylic ester derivatives and dibuprenorphine
dicarboxylic ester derivatives, which exert a longer
10 analgesic effect as compared to buprenorphine
hydrochloride. The invention also relates to processes for
preparing the novel ester derivatives of buprenorphine, and
long-acting analgesic pharmaceutical compositions
containing a compound selected from buprenorphine base and
15 the novel ester derivatives of buprenorphine.

2. Description of the Related Art

 Prolonged analgesia is particularly desirable in
patients suffering from moderate to severe pain, such as
postoperative pain and cancer pain. Currently, local
20 anesthetics, weak analgesics and potent analgesics are used
in this field, but they are all short-acting drugs.

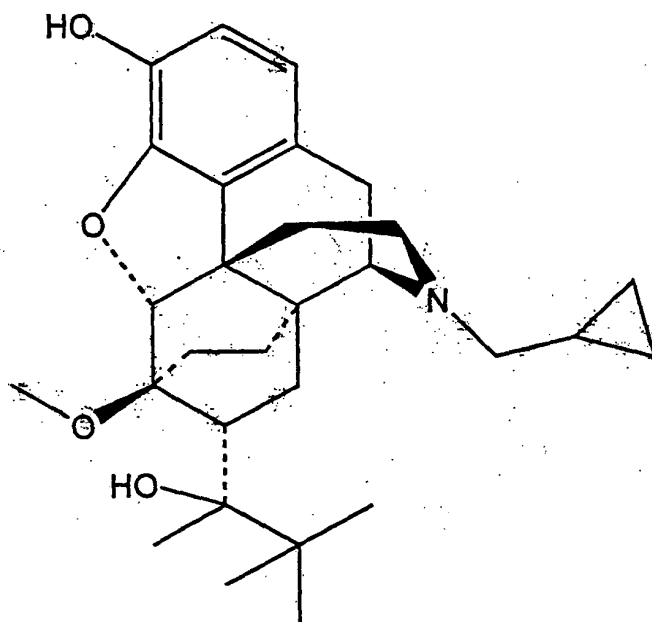
 Local anesthetics, e.g., xylocaine or bupivacaine,
relieve some types of pain but they can only be applied to
restricted areas. In addition, local anesthetics are
25 short-acting and exhibit a duration of action normally no
more than 6 hours even when introduced intrathecally.
Therefore, local anesthetics are not satisfactory for the

relief of acute and severe pain caused by cardiac, pulmonary, abdominal, orthopedic and obstetrical surgery, severe burn injury, and terminal stage of cancer.

Weak analgesics, such as acetaminophen and nonsteroidal
5 anti-inflammatory agents (NSAID), relieve pain of only low intensity, such as pain due to headache or toothache, but they do not help in the case of severe pain.

For the pain of high intensity and widespread in origin, potent analgesics, such as morphine, meperidine and
10 fentanyl, are used. They interact with specific opioid receptors (i.e. μ receptors) in the central nervous system (CNS) and exhibit potent analgesic activity. However, all the opioid analgesics exhibit common disadvantages (Hayes, A. G. et al., *Br. J. Pharmacol.*, Vol 79, 731, 1983). The
15 most unwanted problem associated with the long-term use of these potent analgesics is the incidence of addiction. In addition, these potent analgesics may induce severe respiratory depression in patients with poor respiratory function. Moreover, these potent analgesics exhibit a
20 relatively short duration of action, i.e. 3-5 hours. Even when they are administered intrathecally, they fail to provide a duration of action that lasts for a period of more than 24 hours. In addition, if a larger dose of such an agent, e.g. morphine of 0.5-1.0 mg/does, is administered
25 intrathecally to provide a prolonged analgesic effect, fatal respiratory depression is likely to occur (Baxter, A. D. et al., *Can. J. Anesth.*, Vol 36, 503, 1989).

Buprenorphine, the chemical name of which is (5 α ,7 α (S)-17- cyclopropyl-methyl)- α -(1,1-dimethylethyl)-4,5- epoxy- 18,19-dihydro-3-hydroxy-6-methoxy- α -methyl-6,14-ethenomorphinan-7-methanol, is known to be an opioid partial agonist having a potent analgesic effect. Buprenorphine (in free base form), the molecular weight of which is 467.7, is represented by the following formula (A):



(A)

Buprenorphine shares many of the actions of opioid agonists, such as analgesia. The lack of κ agonism accounts for buprenorphine's freedom from the dysphoric and psychotomimetic effects often seen with agonist/antagonist drugs. Other studies suggest that the opioid antagonist effect of buprenorphine may be mediated via an interaction with δ opioid receptors.

Like other potent opioid agonists, buprenorphine produces potent dose-related analgesia. While the exact

mechanism has yet to be fully known, the analgesic effect of buprenorphine appears to arise from a high affinity of buprenorphine for μ opioid receptors in the central nerve system. In addition, buprenorphine may alter the pain threshold (threshold of afferent nerve endings to noxious stimuli). On a weight basis, the analgesic potency of parenteral buprenorphine appears to be about 25 to 50 times as that of morphine, about 200 times as that of pentazocine, and about 600 times as that of meperidine.

Buprenorphine provides several therapeutic advantages in many patients as compared to opioid agonists (e.g., morphine) and mixed agonists-antagonists (e.g., pentazocine, butorphanol, nalbuphine). For example, unlike the mixed agonists-antagonists, buprenorphine has less psychotomimetic effects. When compared with agonists (e.g., morphine and fentanyl), buprenorphine brings about a relatively low risk of respiratory depression.

Buprenorphine has a lesser abuse liability as compared to full agonist opioids. Although infrequent, however, buprenorphine may cause limited physical dependence, and signs and symptoms of mild withdrawal may appear subsequent to discontinuance of a prolonged therapy with buprenorphine alone. Due to buprenorphine's slow dissociation from the μ receptor, elimination of buprenorphine from the CNS is prolonged subsequent to abrupt discontinuance. As a consequence, signs and symptoms due to an acute withdrawal of buprenorphine are less intense than those produced by morphine and occur at a later time.

Buprenorphine, which was disclosed in US 3,433,791 (1968), is sold under the trademarks Buprenex (Morton-Norwich) and Temgesic (Reckitt and Colman), and has been used principally for the management of pain due to surgery, cancer, accidental trauma and myocardial infarction. Buprenorphine has also been used in the detoxification treatment of heroin addicts due to its opioid partial agonist properties (*Bickel, W. K., et al., Chem. Pharmacol. Ther. (1988), 43 (1):72-78; and Fudala, P.J., et al., Clin. Pharmacol. Ther. (1990), 47 (4):525-534*). Buprenorphine has been administered commonly by intramuscular injection or intravenous injection, but the duration of action is only 6-8 hours.

A long-acting analgesic effect is particularly desirable in patients suffering from acute or chronic pain. These pains may last from days to months. For example, acute pain, such as postoperative pain, traumatic pain, and burn pain, may last 4-6 days; chronic pain, such as nonmalignant pain and cancer pain, may last from several weeks to a few months.

In order to control or prolong the duration of action of a target drug during clinical use, there have been developed certain pharmaceutical preparations. In regard to buprenorphine, due to the high level of crystallinity as reflected in the melting point of its free base, 218 °C, buprenorphine is not likely to be a good candidate for transdermal drug delivery by itself. Utilization of hydrochloride salt, along with a permeation enhancer, has

been offered as one solution to obtain sufficient skin permeation of buprenorphine for analgesic purposes. For example, US 6,004,969 disclosed a transdermal delivery preparation of buprenorphine, which consisted of buprenorphine or the hydrochloride salt thereof, pure components from Chinese herbs as transdermal penetration enhancers, and other excipients necessary for transdermal preparations.

A prodrug strategy is another possibility. Stinchcomb et al. reported in *Pharm. Res.* (1995), 12 (10): 1526-1529 six alkyl ester prodrugs of buprenorphine, the synthesis of which started from buprenorphine hydrochloride and involved the reaction of buprenorphine free base, an acid anhydride and 4-dimethylaminopyridine in the presence of dimethylformamide (DMF) as solvent. The physicochemical properties, including hexane solubility, of the six alkyl ester prodrugs of buprenorphine were compared with those of buprenorphine HCl and buprenorphine free base. Stinchcomb et al. further investigated the permeation of buprenorphine and its C₂-C₄ alkyl ester prodrugs through hairless mouse skin and human skin, in which light mineral oil was used as a vehicle in the tested formulations for the permeation experiments (Hirofumi Imoto et al., *Biol. Pharm. Bull.* (1996), 19 (2): 263-267; and Stinchcomb et al., *Pharm. Res.* (1996), 13 (10): 1519-1523).

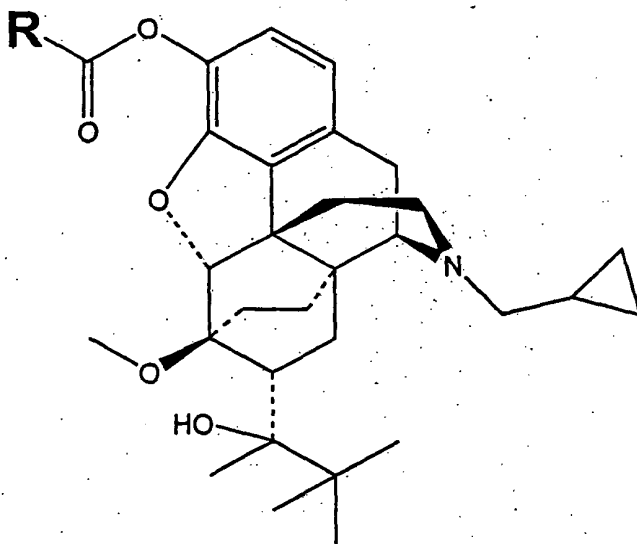
However, no injectable long-acting dosage form of buprenorphine suitable for therapeutic use has been described heretofore. In addition, it is still desirable

to develop new derivatives of buprenorphine which effectively extends the duration of action of buprenorphine *in vivo*.

SUMMARY OF THE INVENTION

5 Therefore, an object of this invention is to provide novel ester derivatives of buprenorphine which have a longer duration of action and same activity as buprenorphine HCl so that they may be used in the treatment of living subjects including humans suffering from severe
10 pain.

In the first aspect, the present invention provides new buprenorphine monocarboxylic ester derivatives of formula (I):



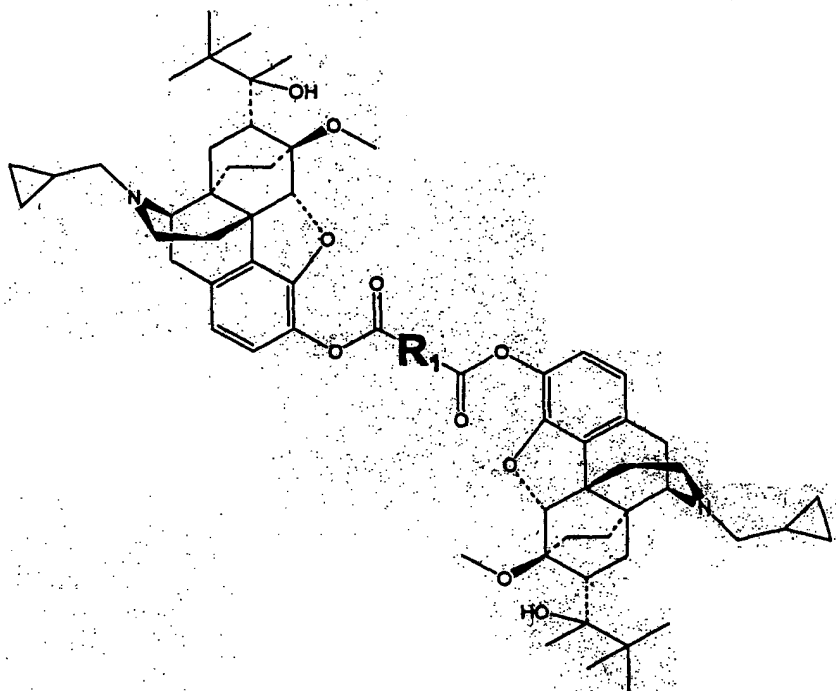
(I)

15 wherein R is selected from the group consisting of a straight-chain or branched saturated or unsaturated aliphatic group optionally substituted with an aryl group, and an aryl group optionally substituted with a straight-chain or branched saturated or unsaturated

aliphatic group;

with the proviso that R is not selected from methyl, ethyl, propyl, n-butyl, n-pentyl, n-hexyl and isopropyl.

In the second aspect, the present invention provides new
 5 dibuprenorphine dicarboxylic ester derivatives of formula
 (II):



(II)

wherein R_1 is a divalent moiety of a saturated or
 10 unsaturated aliphatic group optionally substituted with a
 phenyl group.

In the third aspect, the present invention provides
 processes for preparing the aforesaid novel ester
 derivatives of buprenorphine.

The method of preparing the buprenorphine
 15 monocarboxylic ester derivative of formula (I) includes the
 steps of:

(i) treating buprenorphine HCl or base with

trimethylamine in the presence of methylene chloride; and

(ii) adding to the mixture from step (i) a compound of formula RCOOH , or an acid anhydride or an acid chloride thereof, in the presence of methylene chloride, wherein R in the formula RCOOH is selected from the group consisting of a straight-chain or branched saturated or unsaturated aliphatic group optionally substituted with an aryl group, and an aryl group optionally substituted with a straight-chain or branched saturated or unsaturated aliphatic group.

The method of preparing the dibuprenorphine dicarboxylic ester derivative of formula (II) includes the steps of:

(i') treating buprenorphine HCl or base with trimethylamine in the presence of methylene chloride; and

(ii') adding to the mixture from step (i') a compound of formula $\text{R}_1(\text{COOH})_2$, or an acid anhydride or an acid chloride thereof, in the presence of methylene chloride, wherein R_1 in the formula $\text{R}_1(\text{COOH})_2$ is a divalent moiety of a saturated or unsaturated aliphatic group optionally substituted with a phenyl group.

In the fourth aspect, the present invention provides analgesic pharmaceutical compositions including a buprenorphine monocarboxylic ester derivative of formula (I) or a dibuprenorphine dicarboxylic ester derivative of formula (II) as described above.

In the fifth aspect, the present invention provides an injectable oil suspension which contains a compound

selected from buprenorphine base, a buprenorphine monocarboxylic ester derivative of formula (I), and a dibuprenorphine dicarboxylic ester derivative of formula (II), and which exhibits a longer duration of action when administered intramuscularly or subcutaneously.

BRIEF DESCRIPTION OF THE DRAWING

The above and other features and advantages of the present invention will become apparent in the following detailed description of the preferred embodiments with reference to the accompanying drawing, of which:

Figure 1 shows the ^1H -NMR spectrum chart of buprenorphine enanthate;

Figure 2 shows the mass spectrum chart of buprenorphine enanthate;

Figure 3 shows the UV chart of buprenorphine enanthate;

Figure 4 shows the IR spectrum chart of buprenorphine enanthate;

Figure 5 shows the ^1H -NMR spectrum chart of buprenorphine decanoate;

Figure 6 shows the mass spectrum chart of buprenorphine decanoate;

Figure 7 shows the UV chart of buprenorphine decanoate;

Figure 8 shows the IR spectrum chart of buprenorphine decanoate;

Figure 9 shows the mass spectrum chart of buprenorphine pivalate;

Figure 10 shows the UV chart of buprenorphine pivalate;

Figure 11 shows the IR spectrum chart of buprenorphine

pivalate;

Figure 12 shows the UV chart of buprenorphine palmitate;

Figure 13 shows the IR spectrum chart of buprenorphine palmitate;

5 Figure 14 shows the IR spectrum chart of dibuprenorphine pimelate;

Figure 15 shows the UV chart of dibuprenorphine pimelate;

10 Figure 16 shows the ¹H-NMR spectrum chart of dibuprenorphine sebacoyl ester;

Figure 17 shows the UV chart of dibuprenorphine sebacoyl ester;

Figure 18 shows the IR spectrum chart of dibuprenorphine sebacoyl ester;

15 Figure 19 shows the dose response of intramuscularly administered buprenorphine hydrochloride in rats;

Figures 20-A and 20-B show the dose responses of intramuscularly and subcutaneously administered buprenorphine base in rats, respectively;

20 Figures 21-A to 21-E show the analgesic effects of five intramuscularly administered buprenorphine monocarboxylic ester derivatives of this invention in rats, respectively;

Figure 22 shows the dose response of intramuscularly administered buprenorphine propionate in rats; and

25 Figures 23-A and 23-B show the analgesic effects of two intramuscularly administered dibuprenorphine dicarboxylic ester derivatives of this invention in rats, respectively.

DETAILED DESCRIPTION OF THIS INVENTION

A parenteral solution of buprenorphine hydrochloride (0.3 mg buprenorphine/mL) is commercially available as Buprenex.RTM. (Reckitt & Colman) for intramuscular and intravenous administration. The usual intramuscular or intravenous dose for adults at age over 13 is 0.3 mg every 6 to 8 hours as needed for the relief of moderate to severe pain. The pediatric dose for patients aged 2 to 12 is 2-6 μ g/kg of body weight every 4-6 hours. The mean duration of analgesia is generally six hours following a single intramuscular or intravenous dose of 0.2 to 0.3 mg or 2 to 4 μ g/kg of body weight.

The pharmacokinetics of buprenorphine administered parenterally and sublingually are known. Intravenous administration of a single dose of about 0.3 mg of buprenorphine has been shown to provide mean peak plasma drug concentrations of about 18 ng/mL which occurred within about 2 minutes. Plasma concentrations declined to about 9 and about 0.4 ng/mL after about 5 minutes and about 3 hours, respectively. Following an intramuscular administration of a second 0.3-mg dose 3 hours after the initial intravenous dose, mean peak plasma buprenorphine concentrations of about 3.6 ng/mL occurred within about 2 to about 5 minutes and declined to about 0.4 ng/mL after about 3 hours. Approximately 10 minutes after administration, plasma concentrations of buprenorphine are similar following intravenous or intramuscular injection. It has been previously reported that a usual sublingual analgesic dose of buprenorphine is 0.2 to 0.4 mg every 8 hours (see, e.g.,

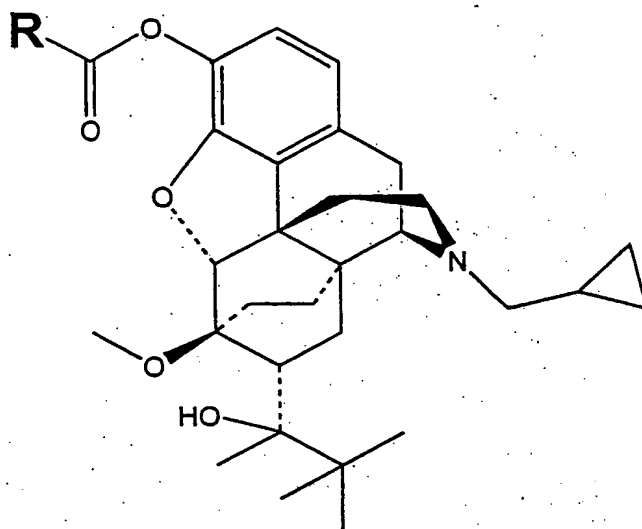
Kuhlman, JJ et al., *J. Analyt. Toxicol.* (1996), 20(10): 369-378). For a 0.4 mg sublingual dose, the C_{\max} was reported as 0.5 ± 0.06 ng/mL; the T_{\max} was reported as 210 ± 40 min; and a systemic availability of $57.7 \pm 6\%$ was also reported.

5 Buprenorphine is almost completely metabolized in the liver, principally by N-dealkylation, to form norbuprenorphine (N-dealkylbuprenorphine). Buprenorphine and norbuprenorphine also undergo conjugation with glucuronic acid. Like the metabolites of other opioid
10 agonists, norbuprenorphine may have weak analgesic activities. However, studies to determine the analgesic activity of the metabolites of buprenorphine have not been performed. Buprenorphine and its metabolites are excreted principally in feces via biliary elimination and also in
15 urine. Buprenorphine is excreted in feces mainly as unchanged drug. Small amounts of norbuprenorphine are also excreted in feces. The drug and its metabolites are believed to undergo enterohepatic circulation. Norbuprenorphine appears to be excreted principally in urine at a slower rate
20 than the parent drug. Total plasma clearance of buprenorphine is reported to be approximately 0.28 L/minute in conscious postoperative patients. Limited data indicate that there is considerable interindividual variability in buprenorphine pharmacokinetics in children. However,
25 clearance of the drug appears to be faster in children (e.g., those 5 to 7 years of age) as compared to that in adults. Optimal dosing interval of buprenorphine may have to be decreased in pediatric patients.

In view of the aforesaid, the Applicant endeavored to prolong the duration of action of buprenorphine and synthesized novel ester derivatives of buprenorphine, which have been proved to have the same analgesic activity as that of buprenorphine HCl. Sustained release pharmaceutical compositions comprising a compound selected from buprenorphine base and the novel ester derivatives of buprenorphine according to this invention were further developed. These compositions were demonstrated to exhibit long-acting analgesic effects of several days with a relatively rapid onset of action (within 2 hours).

Esterification of the phenol group on carbon atom 3 of the morphine ring (the basic structure of morphine, buprenorphine, nalbuphine and the like) enables the esterified derivatives to have the following characteristics: (1) increased lipophilicity; (2) low affinity to morphine receptors; (3) the side effects are decreased, but released parent drugs maintain the same pharmacological activity; and (4) the effect and safety of esterified derivatives and mother compounds remain the same (Broekkamp CL et al., *J. Pharm. Pharmacol*, 1988, 40:434-7).

The present invention provides new buprenorphine monocarboxylic ester derivatives of formula (I):



(I)

wherein R is selected from the group consisting of a straight-chain or branched saturated or unsaturated aliphatic group optionally substituted with an aryl group, and an aryl group optionally substituted with a straight-chain or branched saturated or unsaturated aliphatic group;

with the proviso that R is not selected from methyl, ethyl, propyl, n-butyl, n-pentyl, n-hexyl and isopropyl.

Preferably, R is an alkyl group optionally substituted with a phenyl group.

Preferably, R is an alkyl group having 2 to 40 carbon atoms, and more preferably, an alkyl group having 5 to 20 carbon atoms.

Preferably, R is selected from the group consisting of a straight-chained alkyl group optionally substituted with a phenyl group, a branched alkyl group optionally substituted with a phenyl group, a phenyl group optionally substituted with a straight-chain aliphatic group, and a

phenyl group optionally substituted with a branched aliphatic group.

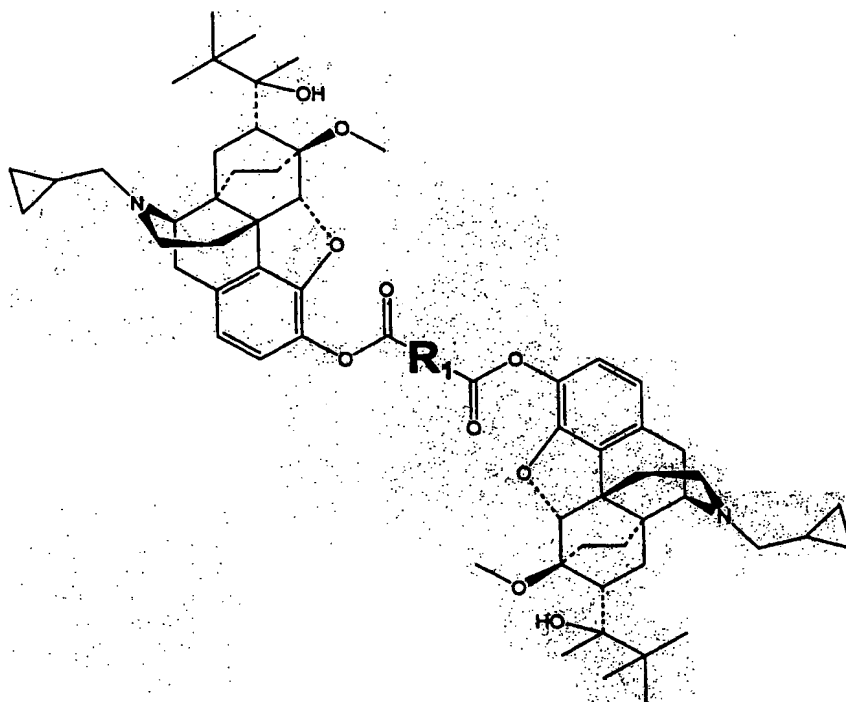
In a preferred embodiment of this invention, R is an alkyl moiety derived from a fatty acid of formula RCOOH.

5 More preferably, R represents an alkyl group optionally substituted with a phenyl and having 2 to 40 (preferably 5 to 20) carbon atoms.

The preferred buprenorphine monocarboxylic esters according to this invention are prepared from buprenorphine
10 and a carboxylic acid selected from the group consisting of: propionic acid, benzoic acid, enanthic acid, n-valeric acid, pivalic acid, decanoic acid; saturated fatty acids, such as lauric acid, palmitoyl acid, stearic acid, arachidic acid and cerotic acid, etc.; and unsaturated
15 fatty acid, such as oleic acid, linolenic acid, undecylenic acid and cinnamic acid, etc.

Preferably, the buprenorphine monocarboxylic ester derivative according to this invention is selected from buprenorphine pivalate, buprenorphine benzoate,
20 buprenorphine decanoate and buprenorphine palmitate.

The present invention also provides new dibuprenorphine dicarboxylic ester derivatives of formula (II):



(II)

wherein R_1 is a divalent moiety of a saturated or unsaturated aliphatic group optionally substituted with a phenyl group.

5 Preferably, the aliphatic group is selected from a straight-chain alkyl group, a branched alkyl group, a straight-chain alkyl group substituted with a phenyl group and a branched alkyl group substituted with a phenyl group. Preferably, the aliphatic group has 1 to 40 carbon atoms,
10 and more preferably, 1 to 20 carbon atoms.

Preferably, R_1 is an alkylene group having 1 to 40 (more preferably, 3 to 20) carbon atoms.

Preferably, the dibuprenorphine dicarboxylic esters according to this invention are prepared from buprenorphine
15 and a C_5 - C_{20} aliphatic dicarboxylic acid.

Preferably, the dibuprenorphine dicarboxylic ester derivative according to this invention is selected from

dibuprenorphine pimelate and dibuprenorphine sebacoyl ester.

Buprenorphine base was prepared from its HCl salt. A given amount of commercial buprenorphine HCl was dissolved in water, followed by the addition of a saturated solution of Na_2CO_3 , to precipitate buprenorphine base. The precipitate was then filtered and washed several times with cold deionized water to remove excess Na_2CO_3 . The white residue was then dried overnight in air. The dried residue was added into a water:ethanol (80:20) mixture, and heated to 60°C , to dissolve the free base, followed by immediate filtration. Upon cooling, the buprenorphine base crystallized. The crystalline product was then filtered and dried under a gentle stream of nitrogen. The purity of the base was checked by the melting point and HPLC assay. The melting point of the base was 209°C , virtually the same as reported in literature. The purity of the base as determined by HPLC assay was 99%.

The buprenorphine monocarboxylic ester derivative of formula (I) can be prepared by a process comprising the following steps:

(i) treating buprenorphine HCl or base with trimethylamine in the presence of methylene chloride; and

(ii) adding to the mixture from step (i) a compound of formula RCOOH , or an acid anhydride or an acid chloride thereof, in the presence of methylene chloride, wherein R in the formula RCOOH is selected from the group consisting of a straight-chain or branched saturated or unsaturated

aliphatic group optionally substituted with an aryl group, and an aryl group optionally substituted with a straight-chain or branched saturated or unsaturated aliphatic group.

5 Preferably, an aliphatic carboxylic acid having 1-40 (more preferably, 5-20) carbon atoms, or an acid anhydride or an acid chloride thereof, is used in the above step (ii). More preferably, a saturated C₅-C₂₀ aliphatic carboxylic acid is used in the above step (ii).

10 In a preferred embodiment of this invention, heptanoyl chloride is used in the above step (ii).

 In another preferred embodiment of this invention, decanoyl chloride is used in step (ii).

 In a further preferred embodiment of this invention,
15 pivaloyl chloride is used in step (ii).

 In another further preferred embodiment of this invention, hexadecanoyl chloride is used in step (ii).

 In yet another preferred embodiment of this invention, benzoyl chloride is used in step (ii).

20 The buprenorphine polyester derivative of formula (II) according to this invention can be prepared by a process comprising the following steps:

 (i') treating buprenorphine HCl or base with trimethylamine in the presence of methylene chloride; and

25 (ii') adding to the mixture from step (i') a compound of formula R₁(COOH)₂, or an acid anhydride or an acid chloride thereof, in the presence of methylene chloride, wherein R₁ in the formula R₁(COOH)₂ is a divalent moiety of

a saturated or unsaturated aliphatic group optionally substituted with a phenyl group.

Preferably, an aliphatic dicarboxylic acid having 3-40 (more preferably, 5-20) carbon atoms, or an acid anhydride or an acid chloride thereof, is used in the above step (ii'). More preferably, a saturated C_5-C_{20} aliphatic dicarboxylic acid is used in the above step (ii').

In a preferred embodiment of this invention, heptanedioatyl chloride is used in the above step (ii').

10 In another preferred embodiment of this invention, sebacoyl acid is used in the above step (ii').

To synthesize the buprenorphine ester derivatives represented by formula (I) and formula (II), respectively, buprenorphine HCl or base was dissolved in methylene chloride, followed by the addition of a solution of triethylamine in methylene chloride. To the mixture was added dropwise a solution of a compound of formula $R(COOH)_2$ or formula $R_1(COOH)_2$ in methylene chloride.

Upon completion of esterification, the resultant product was purified by passing through a silical gel column, and a buprenorphine ester derivative represented by formula (I) or formula (II) was obtained.

As an alternative, the buprenorphine ester derivatives of this invention may be obtained by the general method of preparing esters from alcohols or phenols, for instance, by reacting the hydroxyl group of buprenorphine with acid chlorides, acid anhydrides, esters or sulfonyl chlorides of the compound formula $R(COOH)_2$ or formula $R_1(COOH)_2$.

The buprenorphine ester derivatives synthesized by the methods described above have been identified by nuclear magnetic resonance (NMR), infrared (IR) and ultraviolet (UV) spectroscopy, gas chromatography/mass spectrometry (CG/MS), and elementary analysis.

The buprenorphine ester derivatives may be formulated into different dosage forms as desired.

In general, to achieve the long acting therapeutic efficacy of a target, various dosage forms may be prepared in which the target drug is esterified or dissolved in an oil vehicle to form a parenteral formulation, so that upon being administered to the human or animal body, the release rate of the target drug may slow down due to the influence of some factors, such as the increased solubility of the target drug in oil. In these cases, the dosing interval of the target drug can be set longer by virtue of the prolonged duration of action thereof.

Gelders reported in *Int. Clin. Psychophacol* (1986), volume 1, page 1, and Hinko, C.N. et al. reported in *Neuropharmacology* (1998), volume 27, page 475, the formation of a controlled-release dosage form of haloperidol decanoate in injectable oil, such as sesame oil or soybean oil, the analgesic effect of which was prolonged due to the extended dosing interval from 2 to 4 times a day to 1 to 2 times a month.

Norman T.R. reported in *Int. Clin. Psychopharmacol.* (1987), Volum 2, pp. 299-305, the preparation of fluphenazin decanoate from fluphenazin. Hinko, C.N.

reported in *Neuropharmacology* (1988), volume 27, pp. 475-483, the preparation of an ester of nipectic acid. Broekkamp C.L. reported in *J. Pharm. Pharmacol.* (1988), Vol. 40, pp. 434-437, the preparation of nicotinoyl morphine ester from morphine. Joshi, J.V. et al. reported in *Steroids* (1989), volume 53, pp. 751-761, a precursor preparation of northisterone enenthate, which could be set with a longer dosing interval of up to two months.

However, due to unknown factors present in nature, quick release of a target drug from an oil vehicle could sometimes occur. For instance, the release of testosterone from the intramuscular administration of a testosterone suspension was found to be quick (Tanaka, T., *Chem. Pharm. Bull.* (1974), Vol. 22, pp. 1275-1284). Titulaer, H.A.C. reported the addition of artemisinin in parenteral oil to form various dosage forms for intramuscular, intravenous, oral or rectal administration. However, the drug was released quickly from such dosage forms (*J. Pharm. Pharmacol.* (1990), Vol. 42, pp. 810-813). Zuidema, Z. et al. reported in *International J. of Pharmaceutics* (1994), Vol. 105, pp. 189-207, that the release rate and extent of dosage forms for parenteral administration are very erratic and variable.

According to the aforementioned studies, a dosage form which contains a pharmaceutical composition suspended, or dissolved in an oil vehicle does not certainly exhibit a longer duration of therapeutic effect. In general, any attempt to add a target drug into an oil vehicle for the purpose of obtaining long-acting dosage forms need to take

into account the physical solubility, stability, and release rate of the target drug from such vehicle.

In view of the aforesaid, in order to achieve the goal of extending the duration of action of buprenorphine, the Applicant provided in this application an analgesic pharmaceutical preparation which comprises an injectable oil containing a compound selected from buprenorphine base, a buprenorphine monocarboxylic ester derivative of formula (I), and a dibuprenorphine dicarboxylic ester derivative of formula (II) as described above, in admixture with an injectable oil, and optionally a pharmaceutically acceptable excipient. This preparation permits the compound contained therein to have a longer duration of action in relieving pain.

The suitable injectable oil for use in this invention, which acts as a vehicle for injection preparations, includes, e.g. sesame oil, soybean oil, castor oil, cotton seed oil, peanut oil or ethyl ester of peanut oil, or a combination thereof. The injectable oil preparations can be administered via the intramuscular and subcutaneous routes.

The present invention also provides a process for preparing a long-acting dosage form for buprenorphine base and the novel buprenorphine ester derivatives according to this invention, in which buprenorphine base, or a buprenorphine ester derivative of formula (I) or (II) as described above, is admixed with an injectable oil vehicle, optionally with the addition of pharmaceutically

acceptable excipient(s) commonly employed in the manufacture of medicaments, to thereby form a controlled-release dosage form.

5 According to this invention, the pharmaceutically acceptable excipient, if present, may be selected from benzyl alcohol or chlorobutanol or a combination thereof.

The long-acting parenteral dosage form of this invention can be administered once for several days. Even when long-acting parenteral dosage form of this invention was
10 administered with a larger amount, the occurrence of undesired effects was minimized.

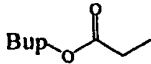
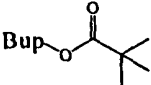
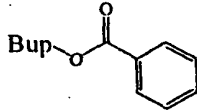
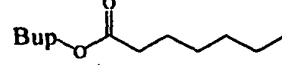
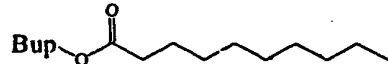
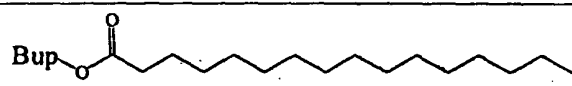
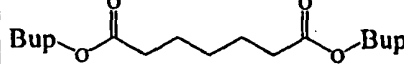
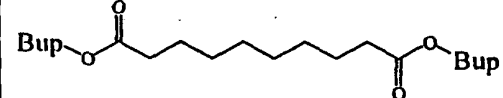
As described above, the advantages of the present pharmaceutical composition include a prolonged duration of action, a rapid onset of action (within 2 hours) and safety
15 that should improve therapeutic quality. The present pharmaceutical composition can be set with a dosing interval of several days instead of 6-8 hours for patients suffering from pain.

20 **Examples:**

The following examples are given for the purpose of illustration only and are not intended to limit the scope of the present invention.

The following Table 1 shows the chemical structures of
25 the preferred buprenorphine ester derivatives according to this invention .

Table 1. The molecular structures of buprenorphine HCl, buprenorphine base and the ester derivatives of according to this invention

Compound	Molecular structure
Buprenorphine HCl	Bup · HCl
Buprenorphine base	Bup
Buprenorphine propionate	
Buprenorphine pivalate	
Buprenorphine benzoate	
Buprenorphine enanthate	
Buprenorphine decanoate	
Buprenorphine palmitate	
Dibuprenorphine pimelate	
Dibuprenorphine sebacoyl ester	

Bup: Buprenorphine

5 The buprenorphine ester derivatives listed in Table 1 can be synthesized by suitable known methods, such as those disclosed in U.S. Patent Nos. 5,750,534 and 6,225,321.

Synthesis Ex. 1 Preparation of buprenorphine enanthate

10 75 mL of methylene chloride (Mallinckrodt, Baker, U.S.A.) and 0.01 mole of buprenorphine HCl or base were added into a 250-mL round-bottomed flask which was placed in an ice bath for cooling. The mixture was stirred and 20 mL of methylene chloride containing 0.03 mole of triethylamine

15 (Sigma, MO, U.S.A.) was gradually added thereto. With rapid stirring, another 20 mL of methylene chloride containing

0.011 mole of heptanoyl chloride (Aldrich, Milwaukee, U.S.A) was added dropwise. Thereafter, the mixture was stirred at room temperature for 1 hour. 20 mL of a 10% sodium carbonate solution was then added to neutralize the residual acid and remove water-soluble impurities. Sodium sulfate was used to dehydrate the solution. After drying under vacuum, the title compound, i.e. buprenorphine enanthate, was obtained. The product was purified by column chromatography.

The production of the title compound was affirmed by Figures 1, 2, 3 and 4, which show the ^1H -NMR spectrum chart, the mass spectrum chart, the UV chart, and the IR chart of the title compound, respectively.

Detected properties of the title compound:

Representative ^1H -NMR (400MHz, CDCl_3):
 6.71 (d, 1H, J=8.1Hz), 6.52 (d, 1H, J=8.0Hz), 5.83 (s, 1H),
 4.35 (s, 1H), 3.40 (s, 3H), 2.99-2.80 (m, 3H), 2.59-2.43 (m, 3H),
 2.28-1.59 (m, 11H), 1.35-0.41 (m, 33H).

Representative mass fragments (amu): 580, 564, 523, 490, 478, 464, 378, 113, 84, 55 (detection was carried out using GC-MS spectroscopy (Spectrum RXI, Perkin Elmer, UK)).

Representative IR absorption (cm^{-1}): 3441.2, 3076.6, 2929.9, 1763.2, 1610.8 (detection was carried out using FT-IR spectroscopy (Spectrum RXI, Perkin Elmer, UK)).

Furthermore, the physical characteristics of the title compound are shown in the following Table 2.

Synthesis Ex. 2 Preparation of buprenorphine decanoate

The title compound was prepared according to the

procedures set forth in the above Synthesis Ex. 1, except that 0.011 mole decanoyl chloride (Fluka, Buchs, Switzerland) was used in place of heptanoyl chloride. Pure buprenorphine decanoate was obtained (see Figures 5, 6, 7 and 8, which show the ^1H -NMR spectral chart, the mass spectral chart, the UV chart, and the IR chart of the title compound, respectively).

Detected properties of the title compound:

	Representative	^1H -NMR	(400MHz,	CDCl_3):
10	6.76 (d, 1H, J=8.0Hz),	6.58 (d, 1H, J=8.1Hz),	5.91 (s, 1H),	
	4.41 (s, 1H),	3.45 (s, 3H),	3.00 (m, 2H),	2.87 (m, 1H),
	2.50 (t, 2H, J=7.4Hz),	2.33-2.10 (m, 5H),	2.00-1.78 (m, 4H),	
	1.72-1.66 (m, 4H),	1.37-1.25 (m, 18H),	1.04 (m, 11H),	
	0.87 (t, 3H, J=6.6Hz),	0.80 (m, 1H),	0.69 (m, 1H),	0.48 (m, 2H),
15	0.11 (m, 2H).			

Representative mass fragments (amu): 622, 607, 565, 533, 521, 507, 380, 55 (detection was carried out using GC-MS spectroscopy (Spectrum RXI, Perkin Elmer, UK)).

Representative IR absorption (cm^{-1}): 3448.0, 3076.4, 2927.1, 1763.8, 1610.7 (detection was carried out using FT-IR spectroscopy (Spectrum RXI, Perkin Elmer, UK)).

Furthermore, the physical characteristics of the title compound are shown in the following Table 2.

25 Synthesis Ex. 3 Preparation of buprenorphine pivalate

75 mL of methylene chloride and 0.01 mole of buprenorphine HCl or base were placed in a 250-mL ice-bathed round-bottomed flask. 0.011 mole of pivaloyl chloride

(Acros, New Jersey, U.S.A.) dissolved in 20 mL of methylene chloride was added gradually into the flask while stirring. Following the procedures as described in the above Synthesis Ex. 1, pure buprenorphine pivalate was obtained (see Figures 9, 10 and 11, which show the mass spectral chart, the UV chart, and the IR chart of the title compound, respectively).

Detected properties of the title compound:

Representative mass fragments (amu): 552, 537, 519, 495, 463, 451, 436, 84, 57 (detection was carried out using GC-MS spectroscopy (Spectrum RXI, Perkin Elmer, UK)).

Representative IR absorption (cm^{-1}): 3439.2, 3077.1, 2976.6, 1753.0, 1610.2 (detection was carried out using FT-IR spectroscopy (Spectrum RXI, Perkin Elmer, UK)).

Furthermore, the physical characteristics of the title compound are shown in the following Table 2.

Synthesis Ex. 4 Preparation of buprenorphine palmitate

The title compound was prepared according to the procedures set forth in the above Synthesis Ex. 1, except that 0.011 mole hexadecanoyl chloride (Aldrich, Milwaukee, U.S.A.) was used in place of heptanoyl chloride. Pure buprenorphine palmitate was obtained (see Figures 12 and 13, which show the UV chart and the IR chart of the title compound, respectively).

Detected properties of the title compound:

Representative IR absorption (cm^{-1}): 3447.0, 3076.9, 2924.0, 1763.3, 1610.9 (detection was carried out using

FT-IR spectroscopy (Spectrum RXI, Perkin Elmer, UK)).

Furthermore, the physical characteristics of the title compound are shown in the following Table 2.

5 **Synthesis Ex. 5 Preparation of dibuprenorphine pimelate**

The title compound was prepared according to the procedures set forth in the above Synthesis Ex. 1, except that 0.006 mole heptanedioatyl chloride (Aldrich, Milwaukee, U.S.A.) was used in place of heptanoyl chloride.

10 Pure dibuprenorphine pimelate was obtained (see Figures 14 and 15, which show the IR chart and the UV chart of the title compound, respectively).

Detected properties of the title compound:

Representative IR absorption (cm^{-1}): 3435.0, 3077.0,
15 2953.0, 1760.8, 1611.0 (detection was carried out using FT-IR spectroscopy (Spectrum RXI, Perkin Elmer, UK)).

Furthermore, the physical characteristics of the title compound are shown in the following Table 2.

20 **Synthesis EX. 6 Preparation of dibuprenorphine sebacoyl ester**

The title compound was prepared according to the procedures set forth in the above Synthesis Ex. 1, except that 0.006 mole sebacoyl chloride (Eluka, Buchs, Switzerland) was used in place of heptanoyl chloride. Pure
25 dibuprenorphine sebacoyl ester was obtained (see Figures 16, 17 and 18, which show the ^1H -NMR spectral chart, the UV chart, and the IR chart of the title compound,

respectively).

Detected properties of the title compound:

Representative $^1\text{H-NMR}$ (400MHz, CDCl_3):
 6.75 (d, 2H, $J=8.0\text{Hz}$), 6.57 (d, 2H, $J=8.0\text{Hz}$), 5.90 (s, 2H),
 4.40 (s, 2H), 3.44 (s, 6H), 2.99 (m, 4H), 2.87 (m, 2H),
 2.59 (m, 2H), 2.50 (t, 4H, $J=7.6\text{Hz}$), 2.32-2.23 (m, 8H),
 2.10 (m, 2H), 2.00-1.66 (m, 16H), 1.36-1.26 (m, 18H), 1.05-
 1.01 (m, 22H), 0.80 (m, 2H), 0.69 (m, 2H), 0.47 (m, 4H),
 0.10 (m, 4H).

Representative IR absorption (cm^{-1}): 3435.3, 3077.2,
 2931.9, 1760.0, 1611.3 (detection was carried out using
 FT-IR spectroscopy (Spectrum RXI, Perkin Elmer, UK)).

Furthermore, the physical characteristics of the title
 compound are shown in the following Table 2.

Table 2. The physical characteristics of buprenorphine HCl, base, and its ester derivatives

Compound	MW	MF	MP (°C)	Ester linkage IR(cm^{-1})
Buprenorphine HCl	504.11	$\text{C}_{29}\text{H}_{41}\text{NO}_4 \cdot \text{HCl}$	279~281	—
Buprenorphine base	467.65	$\text{C}_{29}\text{H}_{41}\text{NO}_4$	208~210	—
Buprenorphine propionate	523.72	$\text{C}_{32}\text{H}_{45}\text{NO}_5$	133~135	1765.6
Buprenorphine pivalate	551.77	$\text{C}_{34}\text{H}_{49}\text{NO}_5$	141~143	1753.0
Buprenorphine benzoate	571.76	$\text{C}_{36}\text{H}_{45}\text{NO}_5$	168~170	1742.1
Buprenorphine enanthate	579.83	$\text{C}_{36}\text{H}_{43}\text{NO}_5$	84~86	1763.2
Buprenorphine decanoate	621.91	$\text{C}_{39}\text{H}_{49}\text{NO}_5$	87~89	1763.8
Buprenorphine palmitate	706.07	$\text{C}_{43}\text{H}_{71}\text{NO}_5$	< 0	1763.3
Dibuprenorphine pimelate	1059.45	$\text{C}_{63}\text{H}_{90}\text{N}_2\text{O}_{10}$	103~105	1760.8
Dibuprenorphine sebacoyl ester	1101.53	$\text{C}_{68}\text{H}_{96}\text{N}_2\text{O}_{10}$	89~90	1760.0

Infra-red spectrum of each compound was detected using FT-IR spectroscopy (Spectrum RXI, Perkin Elmer, UK)

Preparation Ex. 1 Preparation of injectable oil formulations containing buprenorphine base or buprenorphine ester derivatives of this invention

5 (1) 10 μ Mole of buprenorphine base was added into 1 mL of sesame oil. The mixture was shaken slightly to effect complete dissolution.

(2) 20 μ Mole of buprenorphine propionate was added into 1 mL of sesame oil. The mixture was shaken slightly to effect
10 complete dissolution.

(3) 20 μ Mole of buprenorphine decanoate was added into 1 mL of sesame oil. The mixture was shaken slightly to effect complete dissolution.

(4) 20 μ Mole of buprenorphine pimelate was added into
15 1 mL of sesame oil. The mixture was shaken slightly to effect complete dissolution.

(5) 20 μ Mole of buprenorphine ester or polyester was added into 1 mL of ethyl ester of peanut oil or soybean oil. The mixture was shaken slightly to effect complete
20 dissolution.

Pharmacological Example 1

In vivo analgesic efficacy of buprenorphine hydrochloride via intramuscular injection (dose-finding
25 study)

(1) Animal: male Sprague-Dawley rats (175-225 gm, 6 weeks old), n=6 in each group.

(2) Drugs: buprenorphine hydrochloride solution in 0.9%

saline, 0.02 μ Mole/kg (=0.01 mg/kg), 0.06 μ Mole/kg (=0.03 mg/kg), 0.18 μ Mole /kg (=0.09 mg/kg), 0.6 μ Mole/kg (=0.3 mg/kg), intramuscular injection in a tested rat's right hind leg.

5 (3) Test: plantar test, using the device (7370, UGO, BASILE, Italy).

The plantar test enables the researcher to discern a peripherally mediated response to thermal stimulation caused by drugs in the unrestrained rat. It basically
10 consists of a movable I.R. (infrared) Generator placed below a glass pane upon which the operator deposits the rat. A Perspex enclosure defines the space within which the animal is unrestrained. It is divided into three compartments, which help the operator to carry out a rapid
15 "screening" work: up to three rats can be tested with no appreciable delay therebetween.

The operator positions the I.R. Generator directly beneath the hind paw of the rat and activates via a START key both the I.R. Source and a reaction time counter. When
20 the rat feels pain and withdraws its paw, the I.R. Generator is automatically switched off and the timer stops, determining the withdrawal latency.

Concerning the detail of the plantar test, reference may be made to, e.g., K.M. Hargreaves et al., "A New and
25 Sensitive Method for Measuring Thermal Nociception in Cutaneous Hyperalgesia," Pain 32:77-88, 1988, and K. M. Hargreaves et al., "Peripheral Action of Opiates in the Blockade of Carrageenan-Induced Inflammation" Pain

Research and Clinical Management, Vol. 3. Elsevier Science Publishers, Amsterdam: 55-60, 1988.

The latency from the time of stimulus (radiant heat) to paw (left hind leg) withdrawal was assigned as response latency. Radiant heat was set to provide a predrug latency of 7-9 seconds. To prevent tissue damage, a 25-second cut-off time was set.

(4) Statistics: Data are shown as mean. "*" means $P < 0.05$ when compared to pretest value using ANOVA and Dunnett test. ANOVA is analysis of variance frequently, abbreviated as ANOVA, and is an extremely powerful statistical technique which can be used to separate and estimate the different causes of variation. Dunnett test is a posterior comparison among means following an ANOVA. This test allows one to make all possible comparisons among groups. P means probability, in which $P < 0.05$ means significantly different in statistics.

(5) Results: Buprenorphine HCl of different doses demonstrated a duration of analgesic action of 3-5 hr (see Table 3 and Figure 19).

Pharmacological Example 2

In vivo dose-finding studies of buprenorphine base via either intramuscular or subcutaneous injection

- (1) Animal: male Sprague-Dawley rats (175-225 gm) (n=6)
- (2) drugs: buprenorphine base in sesame oil, 0.6 $\mu\text{M/kg}$, 6 $\mu\text{M/kg}$, 60 $\mu\text{M/kg}$; intramuscular injection in a tested rat's right hind leg.

(3) Test: plantar test (see Pharmacological Example 1 described above).

(4) Statistics: ANOVA followed by Dunnett test. Data are shown as "means."

5 (5) Results: Buprenorphine base of different doses via intramuscular injection demonstrated a duration of analgesic action of 48-50 hours (see Table 3 and Figure 20-A). Likewise, buprenorphine base of different doses via subcutaneous injection demonstrated a duration of action
10 of 48-50 hours (see Table 3 and Figure 20-B).

Pharmacological Example 3

In vivo analgesic efficacies of five buprenorphine monocarboxylic ester derivatives of formula (I) via
15 intramuscular injection

(1) Animal: male Sprague-Dawley rats (175-225 gm), n = 6 in each group.

(2) drugs: buprenorphine propionate 0.6 μ M/kg, buprenorphine pivalate 0.6 μ M/kg, buprenorphine enanthate
20 0.6 μ M/kg, buprenorphine decanoate 0.6 μ M/kg, and buprenorphine palmitate 0.6 μ M/kg. All of these ester derivatives were dissolved in sesame oil as an oil solution and injected intramuscularly in the right hind leg.

(3) Test: plantar test (see Pharmacological Example 1
25 described above).

(4) Statistics: ANOVA followed by Dunnett test (see Pharmacological Example 1 described above).

(5) Results: Intramuscular injection of the tested five

buprenorphine monocarboxylic ester derivatives of this invention at a dose of 0.6 μ M/kg demonstrated a rapid onset of action with a duration of 48-96 hours, and in particular, both buprenorphine decanoate and palmitate could provide
5 a duration of action of 96 hours (see Table 3 and Figures 21-A to 21-E).

Pharmacological Example 4

In vivo dose-finding studies of buprenorphine propionate via intramuscular injection
10

(1) Animal: male Sprague-Dawley rats (175-225 gm), n = 6 in each group.

(2) drugs: buprenorphine propionate (oil solution), dose: 0.6 μ M/kg, 6 μ M/kg, 60 μ M/kg; intramuscular
15 injection in a tested rat's right hind leg.

(3) Test: plantar test (see Pharmacological Example 1 described above).

(4) Statistics: ANOVA followed by Dunnett test (see Pharmacological Example 1 described above).

(5) Results: Buprenorphine propionate of different doses via intramuscular injection demonstrated a duration of action of 48-60 hours (see Table 3 and Figure 22).
20

Pharmacological Example 5

In vivo analgesic efficacies of two dibuprenorphine dicarboxylic ester derivatives of formula (II) via intramuscular injection
25

(1) Animal: male Sprague-Dawley rats (175-225 gm), n =

6 in each group.

(2) drugs: Dibuprenorphine pimelate, dibuprenorphine
sebacoyl ester, dose: $0.3 \mu\text{M/kg}$ (oil solution in sesame
oil), intramuscular injection in a tested rat's right hind
5 leg.

(3) Test: plantar test (see Pharmacological Example 1
described above).

(4) Statistics: ANOVA followed by Dunnett test (see
Pharmacological Example 1 described above).

10 (5) Results: Both Buprenorphine pimelate and sebacoyl
ester at a dose of $0.3 \mu\text{M/kg}$ via intramuscular injection
demonstrated a rapid onset of action (2 hours) with duration
of action of 72 and 96 hours (see Table 3 and Figures 23-A
and 23-B).

15 The following Table 3 summarizes the analgesic duration
of buprenorphine and its derivatives in rats using the
plantar test.

20

25

Table 3. The analgesic durations of buprenorphine and its derivatives in rats using the plantar test

Compound	Dose (μ M/kg)	Route of administratio	Analgesic duration (h)
Buprenorphine HCl	0.6	IM	5
Buprenorphine base	0.6; 6; 60	IM	48; 48; 50
Buprenorphine base	0.6; 6; 60	SC	48; 50; 48
Buprenorphine propionate	0.6; 6; 60	IM	48; 54; 54
Buprenorphine pivalate	0.6	IM	48
Buprenorphine benzoate	0.6	IM	72
Buprenorphine enanthate	0.6	IM	72
Buprenorphine decanoate	0.6	IM	96
Buprenorphine palmitate	0.6	IM	96
Dibuprenorphine pimelate	0.3	IM	72
Dibuprenorphine sebacoyl ester	0.3	IM	96

IM: intramuscular, SC: subcutaneous

5 While the present invention has been described in connection with what is considered the most practical and preferred embodiments, it is understood that this invention is not limited to the disclosed embodiments but is intended to cover various arrangements included within the spirit and scope of the broadest interpretation so as to encompass
10 all such modifications and equivalent arrangements.